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| 09/992,128 | 11/05/2001 | Elliot R. Ramberg | 03038-0113<br>(42892-261789) | 1422 |

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| EXAMINER | |
|---|---|
| MYERS, CARLA J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | 3 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/992,128 | Applicant(s) RAMBERG, ELLIOT R. |
|---|---|---|
| | Examiner Carla J. Myers | Art Unit 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

In particular, the first line of the specification should be amended to indicate that the present application is a continuation of 09/633,848 filed 08/07/02, which is a continuation of 09/313,121 filed 5/17/99, now U.S. Patent 6,100,040, which is a continuation of 08/739,069, filed 10/25/96, now U.S. Patent 5,962,226, which claims the benefit of U.S. Provisional Application No. 60/005,938, filed 10/27/95.

2. The disclosure is objected to because of the following informalities:

In claim 3, "hybridizing of a reporter molecule" should be amended to read "hybridizing a reporter molecule".

The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR §1.821(d). See, for example, pages 45 and 46 of the specification.

3. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 are indefinite because the claims are drawn to a method for detecting a target nucleic acid sequence, yet, the claims recite a final step of detecting a PNAS. Therefore, it is not clear as to whether the methods are intended to be limited to ones in which a target nucleic acid is detected or ones in which a PNAS is detected. The claims should be amended to indicate the relationship between detection of the PNAS and detection of the target nucleic acid sequence. Furthermore, it is noted that the claims should be amended to recite the full terminology for the acronym PNAS prior to the first recitation of this acronym, i.e. "protected nucleic acid sequence (PNAS)".

Claims 2 and 3, 8-9 and 11-16 are indefinite over the recitation of "the isolated nucleic acids containing one or more PNAS" because this phrase lacks proper antecedent basis since the claims do not previously refer to an isolated nucleic acid containing one or more PNAS. The claims should be amended to refer to the nucleic acid sequences containing one or more PNAS formed in step b).

Claims 2-3, 8-9 and 11-15 are indefinite over the recitation of "detecting the PNAS". Because these claims include a step of digesting the PNAS to form a PNAS/tail prior to performing the detection step, it is unclear as to whether the detection step is one in which the PNAS is detected or one in which the PNAS/tail is detected.

Claims 16-18 are indefinite over the recitation of "capable of binding" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited protection molecules only have the potential to bind or do

in fact bind a specific nucleic acid sequence. Amendment of the claim to read e.g. "...protection molecule which binds a specific nucleic acid sequence" would obviate this rejection.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection basedbn the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-3, 5, and 7-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Urdea (U.S. Patent No. 4,775,619).

Urdea (see Figure 1 and embodiment 2) teaches a method of detecting a target nucleic acid comprising contacting a sample suspected of containing a target nucleic acid of interest with an immobilized capture probe and a detectably labeled reporter nucleic acid so as form a double stranded nucleic acid sequence (which is considered to be a PNAS). Urdea further teaches nuclease digestion of the PNAS and detection of the presence of the PNAS based upon detection of released detectable labeled reporter nucleic acids (see Figure 1, embodiment 2). Urdea (col. 4, liens 50-55) teaches that this method can be used to detect nucleic acids from microbial and viral sources. The reference teaches that restriction enzymes which cleave the PNAS at a specific site to permit removal

of the detectably labeled reporter group may be used or alternatively, enzymes which permit random hydrolysis of the immobilized PNAS can be used (col. 7, lines 52-63). With respect to claims 16-18, Urdea teaches compositions comprising an immobilized capture molecule and a detectably labeled reporter molecule (col. 19, line 46 through col. 20, line 10). The double stranded and immobilized nucleic acid target is considered to be a PNAS because hybridization of the target nucleic acid to the immobilized capture nucleic acid results in the formation of a complex that is protected from loss of the target by a washing step.

5. Claims 1, 4, and 16-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Cantor (U.S. Patent 5,482,836).

Cantor teaches methods for identifying and isolating double stranded nucleic acid molecules based upon triple helix formation (see abstract and figure 1). Cantor teaches methods in which a double-stranded nucleic acid is contacted with a capture probe to form an immobilized triple helix. Cantor teaches that the use of triplex-affinity capture is an advantageous means for manipulating double-stranded nucleic acids while maintaining the native structure of the nucleic acid (col. 2, lines 47-59 and col. 5 lines 13-37). Cantor teaches applying the method to the isolation and detection of nucleic acids from a human and a yeast library (examples 1 and 2). The triplex target/probe complex is considered to be a nucleic acid molecule comprising a PNAS since binding of the capture probe to the target nucleic acid results in the formation of a complex that is "protected", from e.g. digestion or from loss of the target by a washing step. The triplex target/probe complex of Cantor meets all of the limitations for a PNAS as defined in the specification at pages 7 and 47-49. With respect to

claims 16 and 17, Cantor teaches compositions comprising probes capable of binding a target nucleic acid, biotin/avidin capture moieties (col. 9), and reporter moieties, such as digoxigenin (see col. 12) and thereby teaches compositions comprising a protection molecule, a capture molecule and a reporter molecule.

6. Claims 1-3, and 6-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Sena (U.S. Patent 5,273,881).

Sena teaches methods for detecting the presence of a double-stranded nucleic acid molecule wherein at least one double-stranded probe containing capture and reporter moieties, are hybridized to a target nucleic acid in the presence of the protein RecA and the capture and reporter moieties are used to detect the presence of the target nucleic acid (figure 10, col. 3). In the case in which more than one probe is used, one probe contains a capture moiety and the second probe contains a reporter moiety and each of the probes hybridizes to distinct regions of the double-stranded target nucleic acid (col. 4-5). Sena teaches that the combination of the target nucleic acid and the probe forms a protected nucleic acid sequence because restriction enzyme sites originally present in the target nucleic acid at the site of hybridization of the probe are no longer cleavable after formation of the probe/target complex (figure 15, col. 5, lines 39-50). Alternatively, the combination of the target and probe can create new cleavage sites that are not present in the target nucleic acid alone (col. 5, lines 51-62). The double D target/probe complex of Sena is considered to meet all of the limitations of the PNAS molecule defined in the specification at pages 7 and 47-49. Sena teaches use of lambda phage libraries as a source for the target nucleic acid and teaches that other sources may also

be utilized including microbial and viral sources (col. 8 and 13-14). Sena teaches that the RecA protein may be removed from the target/probe complex prior to detection but that this step is not required so that the PNAS formed by binding of the target nucleic acid to the capture and reporter probes may also comprise a RecA protein component (see col. 4). Sena also teaches methods which include step of capturing a target nucleic acid, digesting target nucleic acid and detecting the presence of a target nucleic acid via a reporter group. With respect to claims 16-18, Sena teaches compositions comprising hybridization probes, capture moieties and reporter moieties (see col. 23-24).

7. Claims 1-3, 5, and 7-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kruse-Muller (U.S. Patent 5,639,609).

Kruse-Muller teaches methods of detecting target nucleic acid molecule comprising an improved capture/reporter system with an optional amplification step (see abstract and col. 1). The reference teaches that the method can be performed in solution prior to immobilization to a solid support via binding to a capture probe or that the hybridization reaction may be performed using an immobilized capture probe (col. 13). Kruse-Muller teaches that the immobilized target nucleic acid/probe complex is hybridized with a second detectably labeled probe and the presence of the labeled probe is detected as indicative of the presence of the target nucleic acid (col. 4). Kruse-Muller teaches reverse transcribing an RNA molecule to form a protected RNA/DNA nucleic acid sequence, which is protected from RNAase degradation (figure 2 and col. 2). The RNA/DNA hybrid of Kruse-Muller is considered to be a protected nucleic acid because it is protected from digestion

with RNAase, and thereby meets all of the limitations of the PNAS molecule defined in the specification at pages 7 and 47-49. The PNAS is then subjected to digestion with RNaseH, hybridization with a capture probe, immobilization onto a solid surface and detection of the immobilized target/capture probe complex using a labeled reporter probe (figure 2). With respect to claims 16-18, Kruse-Muller teaches a composition comprising a capture probe, capture moieties and a reporter probe (col. 24).

8. Claims 1-3, and 6-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Murtagh (U.S. Patent 5,518,901)

Murtagh teaches a method for detecting a target nucleic acid comprising making a PNAS by amplifying a target nucleic acid using a primer bearing a polyuridine tail, treating the amplified nucleic acid with UDG, thereby creating a single-stranded overhang that protects the nucleic acid from digestion with ExoIII, digesting the nucleic acid with ExoIII, hybridizing a detector probe to the digested nucleic acid, hybridizing a capture probe to the digested nucleic acid and detecting the detector probe as indicative of the presence of the target nucleic acid (see abstract, figure 3, col. 7, lines 43-57 and col. 29 lines 24-29). Murtagh teaches the use of these methods to detect a virus and a mycobacterium (col. 16 and 18). With respect to claims 16-18, Murtagh teaches compositions for practicing the detection method wherein the compositions comprise nuclease protecting polyuridine primers, capture molecules and reporter molecules. It is noted that the claims recite the open claim language "comprising" and thereby include the amplification step of Murtagh.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor (U.S. Patent 5,482,836).

Cantor teaches methods for identifying and isolating double stranded nucleic acid molecules based upon triple helix formation (see abstract and figure 1). Cantor teaches methods in which a double-stranded nucleic acid is contacted with a capture probe to form an immobilized triple helix. Cantor teaches that the use of triplex-affinity capture is an advantageous means for manipulating double-stranded nucleic acids while maintaining the native structure of the nucleic acid (col. 2, lines 47-59 and col. 5 lines 13-37). Cantor teaches applying the method to the isolation and detection of nucleic acids from a human and a yeast library (examples 1 and 2). The triplex target/probe complex is considered to be a nucleic acid molecule comprising a PNAS since binding of the capture probe to the target nucleic acid results in the formation of a complex that is "protected", from e.g. digestion or from loss of the target by a washing step. The triplex target/probe complex of Cantor meets all of the limitations for a PNAS as defined in the specification at pages 7 and 47-49. Cantor does not teach the use of triplex affinity capture for the detection and immobilization of microbial or viral nucleic acids. However, the ordinary artisan at the time the invention was made would have

recognized that the triplex affinity capture method of Cantor would have been applicable to nucleic acids from a variety of sources, including microbial and viral sources. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the triplex affinity capture method of Cantor to the detection of nucleic acids from microbial and viral sources in order to have provided an effective method for detecting and isolating nucleic acids from these sources.

10. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea (U.S. Patent 4,775,619) in view of Cantor (U.S. Patent 5,482,836).

Urdea (see Figure 1 and embodiment 2) teaches a method of detecting a target nucleic acid comprising contacting a sample suspected of containing a target nucleic acid of interest with an immobilized capture probe and a detectably labeled reporter nucleic acid so as form a double stranded nucleic acid sequence (which is considered to be a PNAS). Urdea further teaches nuclease digestion of the PNAS and detection of the presence of the PNAS based upon detection of released detectable labeled reporter nucleic acids (see Figure 1, embodiment 2). Urdea (col. 4, liens 50-55) teaches that this method can be used to detect nucleic acids from microbial and viral sources. The reference teaches that restriction enzymes which cleave the PNAS at a specific site to permit removal of the detectably labeled reporter group may be used or alternatively, enzymes which permit random hydrolysis of the immobilized PNAS can be used (col. 7, lines 52-63). With respect to claims 16-18, Urdea teaches compositions comprising an immobilized capture molecule and a detectably labeled reporter molecule (col. 19, line 46 through col. 20, line 10). The double stranded and immobilized

nucleic acid target is considered to be a PNAS because hybridization of the target nucleic acid to the immobilized capture nucleic acid results in the formation of a complex that is protected from loss of the target by a washing step. Urdea does not teach the use of hybridization of a nucleic acid probe to a double-stranded nucleic acid target to form a triplex PNAS.

Cantor teaches methods for identifying and isolating double stranded nucleic acid molecules based upon triple helix formation (see abstract and figure 1). Cantor teaches methods in which a double-stranded nucleic acid is contacted with a capture probe to form an immobilized triple helix. Cantor teaches that the use of triplex-affinity capture is an advantageous means for manipulating double-stranded nucleic acids while maintaining the native structure of the nucleic acid (col. 2, lines 47-59 and col. 5 lines 13-37). Cantor teaches applying the method to the isolation and detection of nucleic acids from a human and a yeast library (examples 1 and 2). The triplex target/probe complex is considered to be a nucleic acid molecule comprising a PNAS since binding of the capture probe to the target nucleic acid results in the formation of a complex that is "protected", from e.g. digestion or from loss of the target by a washing step. The triplex target/probe complex of Cantor meets all of the limitations for a PNAS as defined in the specification at pages 7 and 47-49.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have substituted the double-stranded target nucleic acid of Cantor for the single-stranded target in the methods of Urdea so that hybridization of the probe to the target nucleic acid formed a triplex PNAS rather than a duplex PNAS in order to have achieved the objective of improving the method of Urdea by obviating the need to denature the target nucleic acid prior to performing the

hybridization step. One of ordinary skill in the art would have been motivated to have made such a modification of the method of Urdea in view of the teachings of Cantor that hybridization probes which form triplex structures with double-stranded target nucleic acids are effective for the identification of and isolation of those double-stranded target nucleic acids.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,962,225. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '225 are both inclusive of methods for detecting a target nucleic acid molecule wherein the methods comprise contacting a target nucleic acid molecule with a target protecting molecule to form a PNAS and digesting the PNAS with one or more enzymes to form a 5' single stranded region (PNAS/tail), capturing the PNAS/tail, and detecting the PNAS/tail as indicative of the presence of the target nucleic acid. Furthermore, the instant claims are inclusive of compositions comprising the reagents required to perform the detection method. Thereby, it

would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated the instantly claimed compositions in order to have facilitated practicing the detection method.

12. Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,100,040. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '225 are both inclusive of methods for detecting a target nucleic acid molecule wherein the methods comprise contacting a target nucleic acid molecule with a target protecting molecule to form a PNAS and digesting the PNAS with one or more enzymes to form a 5' single stranded region (PNAS/tail), capturing the PNAS/tail, and detecting the PNAS/tail as indicative of the presence of the target nucleic acid. Furthermore, the instant claims are inclusive of compositions comprising the reagents required to perform the detection method. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated the instantly claimed compositions in order to have facilitated practicing the detection method.

13. Claims 1-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-21 and 39-53 of copending U.S. Application No. 09/633, 848. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '848 are both inclusive of methods for detecting a target nucleic acid molecule wherein the methods comprise contacting a target nucleic

acid molecule with a target protecting molecule to form a PNAS and digesting the PNAS with one or more enzymes to form a 5' single stranded region (PNAS/tail), capturing the PNAS/tail, and detecting the PNAS/tail as indicative of the presence of the target nucleic acid. Furthermore, the instant claims are inclusive of compositions comprising the reagents required to perform the detection method. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated the instantly claimed compositions in order to have facilitated practicing the detection method.

This is a provisional obviousness-type double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

June 24, 2002

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER